

Review

The evolution of ageing

Lucy A.K. Milewski*

Bute Medical Buildings, University of St Andrews, St Andrews, Fife KY16 9TS, UK.

* **Corresponding author:** 5 Picton Close, Crundale, Haverfordwest, Pembrokeshire SA62 4EP, UK. Tel: +44 7802 659923. Email: lucymilewski@gmail.com

Supervisor: Professor Thomas R. Meagher, School of Biology, University of St Andrews, St Andrews, Fife KY16 9TH, UK.

Ageing is one of biology's longstanding enigmas—a problem that has perplexed both medical gerontologists and evolutionary biologists alike. One of the most prominent theories on the biochemical causes of ageing is the telomere-cell senescence theory. This theory proposes that ageing is due to the build up of telomere-induced senescent cells within the body. From an evolutionary standpoint, this system is thought to have evolved via antagonistic pleiotropy. Under this view, ageing is seen as a side effect of the telomere-cell senescence system, with the primary function of it being to defend against cancer. However, there are a number of problems with interpreting the system in this way, and several lines of evidence suggest that it was selected first and foremost to cause ageing. This logically entails the view that ageing is adaptive—an idea that is currently controversial.

Key words: ageing, replicative senescence, evolution, telomeres, mutation accumulation, antagonistic pleiotropy.

Submitted on 14 September 2009; accepted on 17 December 2009

Introduction

It is remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed.¹

Ageing—a progressive decline in physiological functioning—is an old problem in biology.^{2, 3} The enigmatic nature of this problem is highlighted by the fact that immortality is able to be maintained at the cellular level; there is nothing inevitable about ageing. Unlike inorganic matter, organisms are not subject to unavoidable decay; they have the ability to regenerate and renew. Why and how organism's age are thus some of biology's most intriguing questions.

Why organisms age

Numerous theories exist as to why, on a biochemical level, organisms age. A comprehensive review undertaken almost two decades ago by Medvedev⁴ catalogued more than 300 theories of ageing, thus illustrating how complex and multifactorial the process is. Despite such complexity, one theory of ageing has remained prominent in the field since its

inception; the *telomere-cell senescence theory*. This theory posits that ageing is largely due to the accumulation of cells in the body which have undergone cell senescence activation by structures called telomeres.

Telomeres and the end-replication problem

Telomeres are regions of repeat DNA that cap the terminal ends of chromosomes, preventing inter-chromosomal fusion and ligation.⁵ In many organisms, including humans, this repeat sequence is 5'-TAGGG-3'.⁶ Telomeres shorten with each cell division in the majority of somatic cells due to the biochemistry of DNA replication. When a cell undergoes mitosis, its DNA is unwound and replicated by the enzyme DNA polymerase. DNA polymerase, however, is only able to proceed in the 3'–5' direction. To make a complementary strand on the 5'–3' template requires the action of RNA primers. These primers initiate the formation of DNA on the 5'–3' template strand and then DNA polymerase takes over, extending the DNA downstream in the 3'–5' direction. However, the DNA under the very last RNA primer is unable to be replicated because DNA polymerase is unable to synthesize DNA de novo.⁶ This means that, at a minimum, the telomere of the daughter chromosome will be eight nucleotides shorter

than the parent chromosome.⁷ Since the RNA primer is not always at the most distal part of the template strand though, the whole Okazaki fragment can be lost, not just the DNA beneath the RNA primer.⁷ For this reason, an average of ~75 nucleotides is lost during each replication event.⁸

The initial telomere length in a taxon is highly species-specific, and it even varies within a species. In humans, for example, the initial telomere length can vary from about 10⁷ to 20 kb.⁸ Telomere length also varies from chromosome to chromosome and even from one end of a chromosome to the other. It is when telomeres reach a critically short length (which is again species-specific) that cell senescence is induced. In humans, this critical telomere length is on average between 4 and 6 kb long.⁹ It is likely that only one or a few telomeres in the cell must reach this critical length to induce the cell senescence programme.¹⁰ Incidentally, the cell senescence programme can also be activated by factors other than telomeres. Cell senescence activated specifically by telomeres, however, is known as 'replicative senescence'. This term will be used interchangeably with the term 'telomere-cell senescence'.

Finally, it is worth noting that telomerase plays an important role in this elaborate system. Telomerase is the enzyme which extends the ends of telomeres, thereby preventing or slowing the rate of attrition. This ensures that telomeres remained capped and that genomic stability is preserved. Telomerase is active in the germ line and during embryogenesis which ensures that telomere attrition does not continue from generation to generation, but instead is limited to the lifetime of each individual.¹¹ Interestingly, despite not being expressed in the majority of somatic tissues, telomerase is expressed at low levels in many stem cell pools.¹² This low level of telomerase expression delays the rate of stem cell telomere attrition, although it does not prevent it altogether. Thus, stem cell pools are somewhat protected against cell senescence, but they are not immune from it—a factor that has important consequences for ageing.

How telomeres activate cell senescence

The mechanisms of telomere shortening have been discussed, but short telomere length per se does not explain how senescence is induced at the cellular level. A common misconception is that telomere erosion causes cells to malfunction because introns begin to be 'eaten into' during the DNA replication process. This is unlikely to be the case though since at the point of cell senescence, telomeres often have substantial lengths of DNA still remaining. In humans, for example, there are between 4 and 6 kb remaining at the time of cell senescence activation.⁹ Telomeres must thus be mediating cellular senescence via other means.

There is now fairly strong evidence that telomeres primarily mediate cellular senescence via the action of a protein called p53.¹² The C-terminus of p53 is known to recognize and interact with damage to telomeric DNA.⁵ Telomeric damage

is likely to accumulate over time, since telomeres have a specific deficiency in repair enzymes.⁷ Thus p53, being sensitive to telomeric damage, may be activated when the level of this damage reaches a critical point. If this scenario is correct, then short telomeres are purely correlational with the induction of p53. The possibility still remains, however, that short telomeres themselves are recognized as DNA damage by p53.⁵ Under this scenario, telomere shortening is a causative rather than correlative factor in p53 activation. In sum, although the exact mechanisms remain to be fully elucidated, p53 is certainly activated by telomeres.⁵

Once activated, p53 undergoes several modifications, enabling it to accumulate within the nucleus. One of the key post-translational modifications is phosphorylation by the ataxia-telangiectasia protein, which serves to protect p53 from its hdm-2-mediated degradation.⁵ Being a transcription factor, p53 then binds to specific target genes within the nucleus. One of the key target genes that p53 activates is p21, a gene whose protein orchestrates cell cycle arrest. Normally, progression through the cell cycle is dependent on the action of cyclin-dependent kinases. However, the p21 protein inhibits these kinases, thereby preventing the transition of cells from the G1 to the S phase of the cell cycle.⁶ In fact, p21 is able to halt cell cycle progression at both the G1 and the G2 checkpoints of the cell cycle.¹³

Ordinarily, withdrawal from the cell cycle is temporary and cells resume mitosis upon repair of the damaged DNA.⁶ Telomeric-induced p53, however, causes cells to produce proteins that repress the genes required for re-entry into the cell cycle.¹⁰ Such cells are now viewed as 'senescent' and their continued expression of genes inhibiting cell cycle re-entry means they are in a state of permanent growth arrest. These cells are easily recognizable in vitro and in vivo as they adopt a characteristically large phenotype and express biomarkers such as β -galactosidase. They also undergo other complex changes in gene expression pattern and begin to secrete various factors, including inflammatory cytokines, matrix metalloproteinases and growth factors.^{9, 10} These changes are stereotyped and predictable, and Ben-Porath and Weinberg¹⁴ have described cell senescence as a 'fundamental cellular program'.

How cell senescence causes ageing

Senescent cells contribute to organismal ageing in a number of ways. As described above, the level of telomerase activity in stem cells is only enough to slow the rate of telomere attrition; it is not enough to prevent it altogether. This means that over time, stem cells activate cellular senescence and stem cell pools get irreversibly depleted. This leads to a progressive loss of tissue regeneration capacity which ultimately compromises organ architecture and function.¹² It seems that if all somatic stem cells had sufficient telomerase expression to maintain the ends of their telomeres, then indefinite tissue renewal (and therefore an indefinite lifespan) would be possible.¹⁵

Recent evidence that mammalian lifespan is limited by telomerase activity (and therefore telomere attrition rate) comes from a study by Tomás-Loba *et al.*¹⁶ These authors demonstrated that over-expression of telomerase in mice results in longer telomeres and significantly delays ageing. Thus, in wild-type organisms, the low level of telomerase activity and the loss of stem cell pools appear to be responsible for tissue atrophy that occurs during the ageing process. Interestingly, several premature ageing syndromes are characterized by an accelerated rate of telomere attrition¹⁷ and the progeroid disease ‘Werner’s syndrome’ is characterized by a loss of somatic stem cells.¹⁸

Senescent cells also have the potential to generate diverse age-related pathologies. Unlike cells that undergo apoptosis, senescent cells seem refractory to immune clearance meaning they accumulate within tissue.¹⁹ Exactly why such cells are not purged from tissue is unclear,¹⁰ although one possibility is that these cells produce secretions that promote immune evasion.¹⁹ Since senescent cells evade the immune system, they accumulate within the body with age. This accumulation of senescent cells contributes to the ageing phenotype in a number of ways.

Senescent cells undergo a complex change in gene expression pattern. They begin to upregulate a number of protein secretions, some of which include inflammatory cytokines. Inflammatory cytokines mediate local inflammation, and one of the hallmarks of ageing is chronic inflammation.^{12, 19} Senescent cells also secrete matrix metalloproteinases and growth factors, both of which can stimulate cell proliferation and migration; traits that fuel mutations and thus increase the risk of oncogenesis.²⁰ Other secretions from senescent cells have been shown to be capable of inducing the epithelial to mesenchymal transition, a process which confers invasive and metastatic properties on cells. These are defining features of malignancy.¹⁹ There is thus good evidence that senescent cells promote another of the key age-related diseases; cancer.

In fact, senescent cells are likely to be instrumental in many other age-related diseases as well since they are often found in tissues of affected sites, for example, in cases of osteoarthritis and atherosclerosis.¹⁹ Patients of Werner’s syndrome, a progeroid disease whereby ageing is grossly accelerated, also accumulate senescent cells in their tissues prematurely. Again, this is likely to have a causal connection to the ageing-like pathologies they experience so early in life.²¹ In sum, senescent cells remove the tissue’s ability to renew and regenerate, and they accumulate within the body, thereby altering the histologic microenvironment promoting a variety of age-related pathologies.

How ageing evolved

In contrast to biochemical explanations of ageing (which concern questions of *proximate* causality), evolutionary

explanations of ageing concern questions of *ultimate* causality. For the past 50 years, two theories on the ultimate cause of ageing have dominated evolutionary discussions of senescence: the mutation accumulation theory and the antagonistic pleiotropy theory.

The mutation accumulation theory proposes that ageing is due to the build up of deleterious germline mutations—mutations that are only expressed at the latter stages of an organism’s life.²² Since an organism is likely to have died due to predation, disease or natural accidents by these ages, the force of selection is too attenuated to oppose their spread. Ageing is thus able to evolve in even a potentially immortal population by the accumulation of these age-specific mutations over successive generations.

Antagonistic pleiotropy centres on genetic effects that enhance fitness early in life but depress it late in life.¹ Such mutations are able to spread because the force of selection is stronger earlier in life, since more individuals are alive at this stage than at later ages. In sum, both of these theories view ageing as maladaptive, and in neither case is ageing thought to have been *directly* selected for.

The mutation accumulation theory and the antagonistic pleiotropy theory are hypothetico-deductive in nature,²³ meaning that when first conceived they were deduced from assumed laws or premises rather than from empirical observations.²⁴ Hypothetico-deductive theories (by definition) have strong theoretical backing, and indeed the aforementioned theories of ageing were rooted in population genetics several decades ago.^{21, 25, 26} However, these decades witnessed a paucity of research into the biochemistry of ageing. The two mainstream evolutionary accounts of ageing, then, were deeply entrenched in sophisticated theory some time before there was evidence to back them up.

This situation is not problematic as long as theories such as those above function solely as stimuli for research. It is only when such theories are not treated tentatively, but instead prematurely accepted, that problems arise. The reason for this is that when theories are accepted by the scientific community, they become the standard paradigm for the discipline in question. Once a paradigm is established, it begins to dictate how empirical data are interpreted.²⁷ Since hypothetico-deductive theories do not arise from empirical observations, but from assumed laws or premises, it is thus crucially important that they receive empirical verification *before* being used as the standard explanatory tool of the discipline.

With regard to the mutation accumulation theory and the antagonistic pleiotropy theory, it seems that they have been adopted as gerontology’s paradigm largely by default (due to the lack of alternatives) rather than for any compelling evidential reasons. All empirical data are now first and foremost, and almost always, interpreted in the light of one or the other of them. This acceptance has been premature,²⁸ however, and it is clear that accommodation of the telomere system into this mainstream paradigm is strained at best.

Telomeres and evolution

Under traditional evolutionary gerontology, there are only two ways that telomere-induced cell senescence could have evolved, via mutation accumulation or antagonistic pleiotropy. Whether the system is satisfactorily explicable in terms of either of these theories will be explored.

Replicative senescence as a result of mutation accumulation

The mutation accumulation theory assumes that in the wild most organisms are dead before they reach the late ages of life. For this reason, deleterious age-specific alleles can build up, unopposed by selection, to eventually cause ageing. In the light of current knowledge, however, this theory as an explanation of how the telomere system evolved is untenable. The telomere system is complex, hierarchical, integrated and finely regulated. That such sophistication could be the result of unguided mutation accumulation is entirely implausible. Indeed, rather than being indicative of the absence of selection, these features are hallmarks of its moulding hand. As Mitteldorf²⁸ put it, replicative senescence ‘is so transparently deliberate that there can be no doubt of its origin as an adaptation shaped by selection’.

Replicative senescence as a result of antagonistic pleiotropy

Since the mutation accumulation theory is an untenable explanation of replicative senescence, the only other mainstream alternative is antagonistic pleiotropy. Here one must argue that replicative senescence confers an adaptive advantage earlier in life, and that ageing is but an incidental late life side effect of the programme. This is a more viable option, since it grants that the moulding hand of selection has played a role. Not surprisingly, then, this is the position taken by the majority of evolutionary gerontologists. It is proposed that the *primary* function of the telomere system is its role as a natural defence against cancer.²⁹ The basic idea here is that telomere attrition restrains the growth of tumours by limiting the replicative capacities of transformed cells. Once the maximum number of doublings has been reached, telomeres induce cell senescence, thereby permanently removing such cells from the cell cycle. In this way, telomerase repression, by allowing telomere attrition, acts as a barrier to uncontrolled proliferation.¹⁷ Under antagonistic pleiotropy, the later effects of replicative senescence (i.e. ageing) are seen as secondary side effects—effects that have been allowed to persist because selection at older ages is weak.

The hypothesis that telomere-induced cell senescence is instrumental in the suppression of cancer has strong evidence and is uncontroversial.¹⁷ Tumourigenic human cells activate both the p53 and the p21 pathways discussed above,³⁰

and one of the hallmarks of malignancy is the ability to overcome replicative senescence by the reactivation of telomerase.³¹ Thus, replicative senescence (unless subverted) is an effective barrier to malignant transformation. So the telomere-induced cell senescence has a function outside ageing, and this function is adaptive.

Problems with the idea that telomeres evolved as an anti-cancer strategy

It might seem easy to suppose now that the telomere system evolved under antagonistic pleiotropy—having been selected for its beneficial function early in life at the expense of causing ageing later in life.^{29, 32} Although this explanation for how the telomere system evolved is widely accepted, this may largely be due to metaphysical considerations rather than scientific ones. Indeed there are some glaring problems with interpreting the telomere system in this way, all of which are discussed below. The fact that such an interpretation still persists, then, suggests that commitment to the prevailing paradigm has taken precedence over an objective reading of the evidence.

Replicative senescence does not correlate with cancer risk

If replicative senescence evolved as an anti-cancer strategy, one would expect that there is a correlation between the level of telomerase activity and an organism’s risk of cancer. This does hold true for some species such as mice, and in the previously cited study by Tomás-Loba *et al.*,¹⁶ genetically engineered cancer-resistant mice had to be used in order to see the effects of increased telomerase activity. However, there are also examples where this prediction seems patently false. Telomerase activity is high in the somatic tissues of organisms which do not appear to age, such as the rainbow trout and the lobster.^{33, 34} Libertini³⁵ states that the low cancer risk in these organisms is evidenced by the fact they show negligible senescence. High levels of telomerase activity have also been found in several long-lived bird species, including Leach’s storm petrels, again suggesting that high telomerase activity does not correlate with high cancer risk.³⁶ The situation in mammals is similar: some of the longest-lived species within Rodentia such as the naked mole rat and the grey squirrel have high telomerase activity in their somatic tissue.³⁷

As suggested above, these data indicate that high telomerase activity does not pose a great cancer risk. In fact, telomerase can protect against cancer because it maintains telomeric, and thus chromosomal integrity.³⁵ When telomere uncapping occurs, telomeres from different chromosomes begin to fuse, causing genomic instability. This instability disrupts the expression of genes involved in growth control,

which ultimately leads to tumourigenesis.³⁸ Thus, the idea that telomerase activity removes a barrier to oncogenic risk is only half the story; it may remove a barrier, but it simultaneously erects another. This fact is not often discussed in the mainstream literature on ageing.

Replicative senescence is not the only solution to cancer

It is also worth noting that even if telomerase did not serve a protective function, and its increased expression did inevitably lead to cancer, then the above data (where long-lived organisms had high telomerase expression) would suggest that alternative anti-cancer defences exist—defences that do not come at the cost of ageing. Gorbunova and Seluanov³⁷ suggest that body mass may be one important alleviation factor. Small organisms have a reduced probability of spontaneous tumour formation because they possess fewer cells. This may counteract any negative effects of continued telomerase expression.

However, there are likely to be more direct strategies and body mass is likely only part of the story. The fact that organisms such as the grey squirrel and the naked mole rat are able to live for over 20 years, despite high telomerase activity, would indicate that they are utilizing other, telomere-independent, tumour suppressor strategies.³⁷ Such strategies clearly do not come at the cost of accelerated ageing. Additionally, if cancer risk does increase with size, then it is likely that Bowhead whales, which can live for up to 200 years,³⁷ have also evolved additional anti-cancer strategies that do not come at the cost of accelerated ageing.

To bolster the above claim of alternative anti-cancer strategies, it is worth noting that telomere-induced cell senescence is not the only solution to tumourigenesis possible. Tumours are primarily the result of DNA damage, and the accumulation of such damage is not biologically unavoidable. Many organisms show negligible senescence, and even *negative* senescence,³⁹ which indicates that some organisms must possess alternative methods of damage resistance. In fact, a greater investment in DNA repair mechanisms can produce a much longer lived organism. Humans, for example, live much longer than mice because they have much more efficient DNA maintenance and repair mechanisms, a trait which is genetically determined and thus evolutionarily malleable.⁴⁰ Embryonic stem cells also have lower mutation frequencies, which owe to their superior mechanisms of minimizing oxidative stress. As soon as the cells begin to differentiate, however, these repair mechanisms get tuned down.⁴¹ This shows that mutations are not inevitable and that organisms are able to cut the risk of cancer in other ways.

In sum, there are no insurmountable constraints that restrict an organism to using replicative senescence as an anti-cancer strategy. The fact that DNA damage, and thus tumours, can be overcome via other routes that do not come at the cost of ageing suggests that telomere-dependent

senescence has not primarily been selected for its anti-cancer effects. Goldsmith⁴² has noted that within traditional evolutionary gerontology (specifically antagonistic pleiotropy), it is thought to be impossible to evolve a beneficial effect without incurring a cost. Clearly, the evidence does not support this conclusion, however. Organisms can evolve both a long life and alternative anti-cancer defences. The fact that they do not, then, suggests that the telomere system is primarily an ageing mechanism, and its usefulness as a defence against cancer is a secondary function. Thus ageing is best explained as an adaptation rather than an epiphenomenon.

Replicative senescence has features necessary for ageing but not for cancer defence

Following growth arrest, senescent cells undergo complex alterations in their gene expression patterns whereby the transcription and synthesis of many proteins get upregulated.¹⁹ These proteins, which include epithelial growth factors, matrix metalloproteinases and inflammatory cytokines, get secreted into the extracellular environment.²⁹ As described above, such secretions alter the tissue microenvironment and eventually cause tissue decline and organismal ageing. The presence of these cellular secretions also predisposes neighbouring cells, whether normal or premalignant, to malignant transformation.²⁰

It was demonstrated previously that the cell senescence programme looks entirely programmed. This programming also extends to the aforementioned complex post-senescent regulatory changes within the cell. Whether cells have senesced prematurely or not, and regardless of the tissue of origin or the trigger, senescent cells undergo predictable post-secretory changes. This phenotype is under transcriptional control and thus seems every bit a product of selection as the earlier stages of the programme, so much so in fact that it has been likened to programmed cell death.¹⁴ The secretions mentioned above do not seem to play any adaptive role in suppressing tumourigenesis though; to the contrary, they actually promote cancer. This casts doubt on the idea that it was primarily selected for this purpose.

To solve this paradox, it has been argued that all the negative effects of the senescent cell secretions are confined to late life, thereby being largely out of the reach of selection.^{19, 32} First, this claim is far from clear. Senescent cells are able to disrupt the tissue architecture of not only old, but also young (normal) tissues.²⁰ Secondly, regarding oncogenesis, senescent cells are able to stimulate tumour growth within a time frame between several days and several months.⁴³ It is not at all clear that these effects are entirely confined to late ages that are rarely seen in the wild.

Even if one does grant that none of the secretory changes exerts an effect until late in life, *ceteris paribus*, the data would still be better suited to a hypothesis that viewed ageing as a direct product of selection rather than an

epiphenomenon. Popper,⁴⁴ who wrote extensively on the nature of scientific theories, held that explanatory power was a key virtue of any scientific theory. With respect to this criterion, the theory that ageing has been directly selected for is certainly preferable. The secretory changes that cause tissue and organismal decline are not only explained, but they are also predicted under the view that telomere-induced cell senescence is an actual adaptation for ageing, rather than just causing it as a by-product. Indeed, such pre-programmed detrimental effects are inexplicable on the view that replicative senescence is first and foremost a tumour defence strategy. There would be no reason for a tumour suppression mechanism to reprogramme the genome and upregulate noxious secretions. Thus, the theory that ageing has been the direct object of selection (and hence that the primary function of the telomere programme is to cause ageing) has greater explanatory scope than the alternative view that ageing is an epiphenomenon of selection acting on other traits, such as ability to suppress cancer. Indeed, it solves a puzzle that the competing theory leaves unanswered.

The ancestral role of telomeres

One final point worth mentioning is the ancestral role of telomeres. Telomeres are not an exclusively multicellular trait; they are also found in contemporary single-celled organisms such as yeasts and protists.^{18, 28} Although contemporary single-celled organisms have undergone hundreds of millions of years of evolutionary change since the last common ancestor of uni- and multicellular organisms, they are still instructive in this area since unicellularity is ancestral to multicellularity.

In contemporary yeast, telomeres play no role in cancer defence (since single-celled organisms do not develop cancer), but they do mediate ageing. The exact mechanisms of telomeric ageing in these single-celled organisms is different from the telomeric ageing described above, since these organisms do not have a cell senescence programme homologous to the multicellular programme. The important point to note, however, is that telomeres (and the repression of telomerase) are instrumental in ageing in these cells. Given that these organisms do not develop cancer, it is likely that the primary role of the system is to limit the replicative lifespan of the organism. If this is representative of the ancestral function of telomeres, then it would seem hasty to write off an analogous primary function in multicellular organisms.

Summary

The key question of the previous section was whether the telomere-cell senescence programme can be accommodated within the current gerontological paradigm. The mutation accumulation theory cannot explain the telomere-cell senescence system since the latter bears all the hallmarks of active selection. The antagonistic pleiotropy theory is more viable

since it grants that selection has played a role. However, accommodation into this theory is rather forced. A lack of replicative senescence does not necessarily increase the risk of cancer, and even if it did, alternative methods of tumour suppression exist. Given these facts, it is highly unlikely that the reason organisms have evolved a limited lifespan is because this reduces their risk of cancer. Furthermore, senescent cells adopt a phenotype which actually promotes cancer and tissue degeneration. If the system was selected first and foremost as a cancer defence strategy, it is not clear why selection has not altered this post-secretory phenotype, or at least caused the immune system to efficiently remove such cells from the tissue, as it does for apoptotic cells. Finally, the ancestral function of telomere shortening appears to be to cause ageing (not defend against cancer), which suggests that an analogous primary function in multicellular organisms is certainly a possibility.

Conclusion

Mitteldorf²⁸ laments that the antagonistic pleiotropy theory has been 'treated as a fixed framework within which the new data must be accommodated'. It certainly seems the case that the telomere-cell senescence system has been explained as a result of antagonistic pleiotropy not because the data command this interpretation, but because this interpretation is the only one that fits within the mainstream paradigm. Historically speaking, there are many instances where the prevailing scientific paradigm of the day has dictated how data are interpreted. Kuhn went so far as to claim that this was the *normal* process of science. Specifically, he wrote:

Closely examined, whether historically or in the contemporary laboratory, [normal science] seems an attempt to force nature into the preformed and relatively inflexible box that the paradigm supplies. No part of the aim of normal science is to call forth new sets of phenomena; indeed those that will not fit in the box are often not seen at all. Nor do scientists normally aim to invent new theories. . . . Instead, normal scientific research is directed to the articulation of those phenomena and theories that the paradigm already supplies.⁴⁵

Kuhn's statement may have been an overgeneralization, but it is fair to say that it does accurately characterize many parts of scientific endeavour. As highlighted above, the antagonistic pleiotropy theory has generally been used unquestioningly as the explanatory tool and this has led to several fairly significant inconsistencies being overlooked. Le Bourg⁴⁶ notes that one reason such inconsistencies are tolerated is because better theories are not available. However, a number of authors have in fact formulated explanations that lie outside gerontology's contemporary paradigm.^{47–50} These authors propose that ageing has been the direct object of selection; an idea that logically entails the view

that ageing is adaptive. Adaptive explanations of ageing are diverse. For example, Longo⁵⁰ suggests that a death programme has been selected for in yeast because when some members of the population die, remaining individuals are able to enjoy an enhanced nutritional environment and increased growing space. Mitteldorf,⁴⁸ on the other hand, suggests that ageing may have evolved to prevent populations from outgrowing their habitat and food supply, which in turn protects populations from the threat of extinction. Although adaptive theories of ageing such as these describe well the empirical data, they often require group-level selection arguments for their justification, and for this reason, they remain unpopular. Given the empirical discrepancies of the current mainstream theories, though, it would seem hasty to write off any alternatives.

Author biography

Lucy recently graduated from the University of St Andrews with a degree in Evolutionary Biology. Her main interests throughout these four years have been evolution and development. More recently she has become interested in the philosophy of science, and is about to begin an MA in the History and Philosophy of Biology at the University of Exeter.

References

- Williams G (1957) Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 11: 398–411.
- Baudisch A (2008) *Inevitable Aging?: Contributions to Evolutionary-demographic Theory*. Berlin: Springer.
- Bowles J (1998) The evolution of aging: a new approach to an old problem of biology. *Med Hypotheses* 51: 179–221.
- Medvedev Z (1990) An attempt at a rational classification of theories of ageing. *Biol Rev Camb Philos Soc* 65: 375–398.
- Milyavsky M, Mimran A, Senderovich S *et al.* (2001) Activation of p53 protein by telomeric (TTAGGG) repeats. *Nucleic Acids Res* 29: 5207–5215.
- Pollard T, Earnshaw W (2004) *Cell Biology*. Pennsylvania: Saunders.
- Proctor C, Kirkwood T (2002) Modelling telomere shortening and the role of oxidative stress. *Mech Ageing Dev* 123: 351–363.
- Jennings B, Ozanne S, Hales C (2000) Nutrition, oxidative damage, telomere shortening, and cellular senescence: individual or connected agents of ageing? *Mol Gen Metab* 71: 32–42.
- Itahana K, Dimri G, Campisi J (2001) Regulation of cellular senescence by p53. *Eur J Biochem* 28: 2784–2791.
- Campisi J, d'Adda di Fagagna F (2007) Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 8: 729–740.
- Collins K, Mitchell J (2002) Telomerase in the human organism. *Oncogene* 21: 564–579.
- Rodier F, Campisi J, Bhaumik D (2007) Two faces of p53: aging and tumor suppression. *Nucleic Acids Res* 35: 7475–7484.
- Han Z, Wei W, Dunaway S *et al.* (2002) Role of p21 in apoptosis and senescence of human colon cancer cells treated with camptothecin. *J Biol Chem* 277: 17154–17160.
- Ben-Porath I, Weinberg R (2005) The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol* 37: 961–976.
- Shawi M, Autexier C (2008) Telomerase, senescence and ageing. *Mech Ageing Dev* 129: 3–10.
- Tomás-Loba A, Flores I, Fernández-Marcos P *et al.* (2008) Telomerase reverse transcriptase delays aging in cancer-resistant mice. *Cell* 135: 609–622.
- Sedivy J (2007) Telomeres limit cancer growth by inducing senescence: long sought in vivo evidence obtained. *Cancer Cell* 11: 389–391.
- Libertini G (2006) Evolutionary explanations of the 'actuarial senescence in the wild' and of the 'state of senility'. *Sci World J* 6: 1086–1108.
- Coppé J, Patil C, Rodier F *et al.* (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol* 6: 2853–2868.
- Parrinello S, Coppé J, Krtolica A *et al.* (2005) Stromal–epithelial interactions in aging and cancer: senescent fibroblasts alter epithelial cell differentiation. *J Cell Biol* 118: 485–496.
- Opresko P (2008) Telomere ResQue and preservation—roles for the Werner syndrome protein and other RecQ helicases. *Mech Ageing Dev* 129: 79–90.
- Medawar P (1952) *An Unsolved Problem in Biology*. London: H.K. Lewis.
- Rose M (1991) *Evolutionary Biology of Aging*. New York: Oxford University Press.
- Achinstein P (2000) Observation and theory. In Newton-Smith W, ed., *A Companion to the Philosophy of Science*. Malden, MA: Blackwell Publishing Ltd, pp. 325–334.
- Hamilton W (1966) The moulding of senescence by natural selection. *J Theor Biol* 12: 12–45.
- Charlesworth B (1980) *Evolution in Age-structured Populations*. Cambridge: Cambridge University Press.
- Ladyman J (2002) *Understanding Philosophy of Science*. New York: Routledge.
- Mitteldorf J (2004) Aging selected for its own sake. *EER* 6: 1–17.
- Campisi J (2003) Cancer and ageing: rival demons? *Nat Rev Cancer* 3: 339–349.
- Parkinson E, Munro J, Steeghs K *et al.* (2000) Replicative senescence as a barrier to human cancer. *Biochem Soc Trans* 28: 226–233.
- Collado M, Blasco M, Serrano M (2007) Cellular senescence in cancer and aging. *Cell* 130: 223–233.
- Troen B (2003) The biology of aging. *Mt Sinai J Med* 70: 3–22.
- Klapper W, Heidorn K, Kühne K *et al.* (1998) Telomerase activity in 'immortal' fish. *FEBS* 434: 409–412.
- Klapper W, Kühne K, Singh K *et al.* (1998) Longevity of lobsters is linked to ubiquitous telomerase expression. *FEBS* 439: 143–146.
- Libertini G (2008) Empirical evidence for various evolutionary hypotheses on species demonstrating increasing mortality with increasing chronological age in the wild. *Sci World J* 8: 183–193.
- Haussmann M, Winkler D, Huntington C *et al.* (2007) Telomerase activity is maintained throughout the lifespan of long-lived birds. *Exp Gerontol* 42: 610–618.
- Gorbunova V, Seluanov A (2009) Coevolution of telomerase activity and body mass in mammals: from mice to beavers. *Mech Ageing Dev* 130: 3–9.
- Gilley D, Tanaka H, Herbert B (2004) Telomere dysfunction in aging and cancer. *Int J Biochem Cell Biol* 37: 1000–1013.
- Vaupel J, Baudisch A, Dölling M *et al.* (2004) The case for negative senescence. *Theor Popul Biol* 65: 339–351.
- Kirkwood T (2005) Understanding the odd science of aging. *Cell* 120: 437–447.
- Kirkwood T (2005) Asymmetry and the origins of ageing. *Mech Ageing Dev* 126: 533–534.

-
42. Goldsmith T (2008) Evolvability and programmed ageing: a reply to de Grey. *Rejuvenation Res* 11: 847–848.
43. Krtolica A, Parrinello S, Lockett S *et al.* (2001) Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc Natl Acad Sci USA* 98: 12072–12077.
44. Popper K (1972) *Objective Knowledge: An Evolutionary Approach*. Oxford: OUP.
45. Kuhn T (1970) *The Structure of Scientific Revolutions*, 2nd ed. London: University of Chicago Press.
46. Le Bourg E (2001) A mini-review of the evolutionary theories of aging. Is it time to accept them? *Demogr Res* 4: 1–28.
47. Libertini G (1988) An adaptive theory of the increasing mortality with increasing chronological age in populations in the wild. *J Theor Biol* 132: 145–162.
48. Mitteldorf J (2006) Chaotic population dynamics and the evolution of ageing. *EER* 8: 561–574.
49. Dytham C, Travis J (2006) Evolving dispersal and age at death. *Oikos* 113: 530–538.
50. Longo V, Mitteldorf J, Skulachev V (2005) Programmed and altruistic ageing. *Nat Rev Genet* 6: 866–72.
-